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Disease-a-Month

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Coronary Artery Disease

A. CARLTON ERNSTENE

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A. Carlton Ernstene

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ATHEROSCLEROSIS of the coronary arteries is responsible for the largest single group of organic disturbances of the heart and causes more deaths each year than all other forms of heart disease combined. Although there are as yet no measures for preventing or retarding the pathologic changes in the coronary vessels, the past 15 years have brought many additions to our knowledge. These advances have resulted in more accurate diagnosis, improved treatment, and a hopeful attitude concerning the possible fruits of further clinical and laboratory research. In addition, accumulated statistics demonstrate that prognosis, although remaining uncertain in the individual patient, is much less unsatisfactory than was formerly supposed. The most significant development, however, has been a radical change in general thinking about the problem of atherosclerosis. For years, this type of arteriosclerosis had been regarded as a natural process due to aging and the inevitable result of the wear and tear of passing years. So long as this opinion held sway, prevention and treatment appeared impossible. Fortunately, the old concept has been discarded, and for it has been substituted the realization that

atherosclerosis is a metabolic disorder and in all probability a disease of cholesterol metabolism. This change has resulted in an active attack on the problem which already has yielded important information.

THE PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis is characterized by the deposition of lipids, chiefly cholesterol and cholesterol esters, in the intima of the involved vessels. Lipids are insoluble in water and are held in solution in the body only by combining with proteins to form lipoproteins. The lipid deposits in atherosclerotic arteries are derived from the normal lipoproteins of the blood plasma which pass into the vessel wall by filtration and then, because of their unstable chemical state, break down and precipitate the fatty fraction. This is the mechanism of the distinctive intimal foam cell. In an excellent review of the present status of our knowledge of atherosclerosis, Page (1) points out that tissue changes in the affected arteries, such as subendothelial fibroblastic proliferation, defects in the internal elastic lamella, and alterations in the ground substance, often are quite as impressive as the accumulations of lipids and may even precede them. These features may be due to disturbances in the tissue metabolism of the affected arteries, and there is a possibility that they have an important influence on the extent of the fatty deposits. It is possible also that variations occur in the ability of proteins to hold lipids in chemical union and that these variations determine to some degree the amount of vascular damage.

METABOLISM OF CHOLESTEROL.—It was demonstrated some 40 years ago that atherosclerosis can be produced in rabbits by feeding a cholesterol-rich diet. Since that time the role of cholesterol has been the subject of extensive speculation and investigation, and with the aid of technics introduced during the past few years much factual information has been obtained. The cholesterol content of blood serum is the algebraic sum of four processes: absorption from the gastrointestinal tract, synthesis in the body (from acetate and other common materials), excretion, and destruction or conversion (2). Synthesis and destruction occur

chiefly in the liver and far outrank intestinal absorption and excretion in importance. Great changes in the serum cholesterol level usually are the result of alterations in the rate of hepatic destruction rather than in the rates of absorption, synthesis, or excretion. Byers, Friedman, and Rosenman (2) believe that decreased destruction probably is the fundamental cause of all cases of hypercholesteremia. According to their hypothesis, there is in hypercholesteremia a quantitative or qualitative increase in the cholesterol-binding capacity of plasma protein so that less cholesterol is surrendered to the liver for destruction. There is no increase in the rate of cholesterol synthesis, and the ability of the liver to destroy the cholesterol offered for removal remains unchanged. The capacity of the liver to synthesize cholesterol appears to be seriously impaired only by severe hepatocellular disease. Gould (3) demonstrated, however, that feeding dogs 1 Gm. of cholesterol daily for a week resulted in a decrease in the rate of hepatic synthesis, although this was not sufficient to prevent a rise in plasma cholesterol. Under normal conditions, variations in intestinal absorption and excretion have only a minor effect on serum cholesterol concentration in man, but Best and his colleagues (4) observed that feeding beta-sitosterol (the main sterol of cottonseed oil) to human subjects for several weeks results in a significant reduction in the cholesterol level. The decrease is explained by the fact that sitosterol interferes with absorption of cholesterol from the intestinal tract. Whether these findings have a bearing on the problem of human atherosclerosis remains to be determined.

EXPERIMENTAL ATHEROSCLEROSIS.—In 1942, the first production of atherosclerosis in chicks by feeding diets supplemented with cholesterol was reported from Katz's laboratory. Katz and his group have based a broad program of research on this technic and have presented the results of their studies in a recent book (5) and subsequent articles. The cholesterol-induced lesions in chicks can be distinguished from those that develop spontaneously and are of particular importance because they occur not only in the aorta and its larger branches, the sites of spontaneous atherosclerosis, but also in the coronary arteries. When cholesterol feeding is stopped, the plasma cholesterol level promptly falls to

normal and the coronary changes slowly regress, but the cholesterol-induced lesions in the aorta are relatively persistent. Lipotropic factors (choline and inositol) have no effect on either cholesterol-induced or spontaneous lesions. The addition of desiccated thyroid to the diet, however, reduces the incidence and severity of the cholesterol-induced form and hastens the regression of coronary atherosclerosis after cessation of cholesterol feeding. Cholesterol-free, fat-poor diets delay but do not prevent the spontaneous variety of atherosclerosis.

Because it has been suggested repeatedly that the cholesterol-phospholipid ratio in plasma may be an important factor in atherogenesis in man, the possibility of such a relationship in chicks was investigated in Katz's laboratory. Cholesterol feeding caused an elevation of the ratio, but there was no correlation between this increase and the occurrence of cholesterol-induced lesions in the aorta. There was, however, a positive correlation between the degree of accompanying hypercholesteremia and the aortic lesions. In other words, the development of the aortic lesions was governed by the serum cholesterol level and not by the cholesterol-phospholipid ratio. It was subsequently found that, in contradistinction to aortic atherosclerosis, there is a relationship between the cholesterol-phospholipid ratio and atherosclerosis of the coronary arteries. The simultaneous administration of estrogens and a cholesterol-supplemented diet to chicks kept the cholesterol-phospholipid ratio at a normal or nearly normal level and prevented the development of coronary atherosclerosis. It did not prevent hypercholesteremia, the relative constancy of the cholesterol-phospholipid ratio being due to a proportionate rise in plasma phospholipids, and did not inhibit the development of the cholesterol-induced form of aortic atherosclerosis. These observations demonstrate not only the importance of the cholesterol-phospholipid ratio in the genesis of coronary atherosclerosis in chicks but also that in chicks, as in man, atherogenesis proceeds according to different laws in different vascular beds. In further experiments coronary atherosclerosis was induced in chicks by feeding cholesterol for several weeks, after which the administration of estrogens was begun without changing the diet. Within a few weeks there was practically complete disappearance of the coronary lesions.

As in the prophylactic-type experiments, aortic atherosclerosis was not affected. The hypercholesteremia produced by the diet was increased moderately by estrogen, but the accompanying estrogen-induced hyperphospholipemia resulted in a fall in the cholesterol-phospholipid ratio to normal. In harmony with these findings is the fact that mature egg-producing hens are markedly resistant to cholesterol-induced coronary atherosclerosis, apparently because of the protective effect of endogenous estrogen.

A substantial elevation in blood pressure can be produced in chicks by feeding salt (5). The hypertension does not result in atherosclerosis of the cholesterol-induced type nor does it intensify the spontaneously occurring form. Cholesterol feeding of the hypertensive birds, however, results in more severe atherosclerosis than does similar feeding of normotensive controls. These observations indicate that, in chicks, hypertension per se does not cause atherosclerosis but is an intensifying factor in the presence of a specific atherogenic stimulus. Whether the aggravating effect is due to increased passage of lipoproteins into the vessel walls because of increased filtration pressure or is the result of vascular damage induced by the hypertension remains to be determined. Clinical and experimental evidence indicates that foci of vascular injury, however produced, are sites of predisposition for the development of atherosclerotic lesions.

LIPOPROTEINS.—Cholesterol, like other lipids, is held in solution in the plasma in the form of lipoproteins. The protein of the combination belongs to one or the other of two groups, the $alpha_1$ globulins and the $beta_1$ globulins, and the respective compounds are therefore known as alpha lipoproteins and beta lipoproteins. Beta lipoproteins have larger and less dense molecules than the alpha variety and contain about 70 per cent of the cholesterol of normal fasting human plasma. Barr (6) observed that the percentage of total cholesterol present as beta lipoproteins is lower in infants and young adults than in older persons, and is lower in young women than in young men. In survivors of myocardial infarction and in conditions which predispose to early and extensive atherosclerosis, such as diabetes mellitus, nephrosis, and familial xanthomatosis, the percentage carried as beta lipoprotein is as high as or even higher than in older people. Stimulated by these

observations and by the fact that in women after the menopause there not only is a loss of the earlier relative immunity to myocardial infarction but also a rise in the percentage of cholesterol carried as beta lipoprotein to the levels customary in men, Barr and his associates administered estrogen to a group of men and women with advanced atherosclerosis. In every patient there was a decrease in the percentage of cholesterol present as beta lipoproteins and an increase in the percentage carried as alpha lipoproteins. After a few weeks the estrogen caused considerable breast development in the men and temporary loss of potency and sexual drive. Although the results of these experiments are of great interest, it is much too early to advocate the routine administration of estrogen for prophylaxis or therapy of coronary atherosclerosis.

Gofman and his group (7) have done a tremendous amount of work on the fractionation of serum lipoproteins by ultracentrifugation, and they believe that lipoproteins having flotation rates between 12 and 100 Svedberg units are atherogenic. Because of the potential importance of this hypothesis, a controlled co-operative study of the problem is being carried out under the auspices of the United States Public Health Service. Conclusions as to the correctness of Gofman's views should await the results of this investigation.

Diet in human atherosclerosis.—Although direct proof is lacking that cholesterol is the specific atherogenic stimulus in man, there is much indirect evidence of an important relationship between atherosclerosis and the serum cholesterol concentration. Keys (8) points out that in conditions where the serum cholesterol is elevated, such as diabetes, nephrosis, hypothyroidism, and idiopathic hypercholesteremia, there is a tendency to early and severe atherosclerosis. In addition, persons who have coronary heart disease tend to have elevated serum cholesterol values, and there is at least some parallelism between the age trend of cholesterol concentration in the serum and the age trend in the development of atherosclerosis. People in countries where the diet is high in calories and lipids have a greater incidence of atherosclerosis and higher serum cholesterol values than do those living on low-fat, low-calorie diets. Cholesterol feeding experiments in man produce little or no increase in serum cholesterol, but these results are not

comparable to the effect of a high-calorie, high-fat, high-cholesterol diet taken over a span of many years.

Fat-free, cholesterol-free diets cause a prompt fall in serum cholesterol concentration, and the addition of animal or vegetable fat to the diet then results in a return of the cholesterol level to its original value. These observations demonstrate that although the serum cholesterol content is independent of the cholesterol intake in short-term experiments, it is influenced importantly by the amount of fat in the diet. There is no difference in this respect between animal and vegetable fat. At the present time there is no sound basis for placing patients with atherosclerosis on low-cholesterol diets. The optimal diet for normal persons and for those who have coronary atherosclerosis is one which avoids or corrects obesity, supplies not more than 25 or 30 per cent of the total calories by fat, and pays no attention to cholesterol except for the avoidance of an excessive intake (8).

HEREDITY IN HUMAN ATHEROSCLEROSIS.—There is general agreement that heredity is an important factor in the pathogenesis of atherosclerosis, but its exact role has not been investigated adequately and should be thoroughly studied.

CLINICAL ASPECTS OF CORONARY HEART DISEASE

Atherosclerosis of the coronary arteries may affect the heart in a number of ways, and these effects may occur singly or in combination. There may be temporary or permanent anoxia of portions of the myocardium, impairment of the contractile power of one or both ventricles, derangements of the conduction mechanism, or disturbances of cardiac rhythm. The various manifestations of coronary heart disease will be discussed in the following sections with particular reference to diagnosis and treatment.

ANGINA PECTORIS

ETIOLOGY AND PATHOGENESIS.—Angina pectoris is the most common form of coronary heart disease. It is characterized by attacks due to temporary myocardial anoxia which probably affects one or more localized areas of the heart muscle rather than the entire myocardium. Although coronary atherosclerosis is the cause

of the syndrome in the great majority of patients, a few cases are due to other conditions such as high-grade aortic stenosis, free aortic regurgitation, or narrowing of the coronary ostia in syphilitic aortitis. The distinctive feature of the condition is paroxysmal pain or discomfort in the chest which occurs whenever the demands on the heart for work become temporarily greater than can be met by the available coronary blood flow. The attacks may be induced by exertion, emotion, an unusually large meal, sudden exposure to cold, a disproportionate reduction in coronary blood flow during sleep, paroxysmal cardiac arrhythmias, and shock or hypotensive states. Rest, nitroglycerin, and correction of the precipitating factor give prompt relief.

Perhaps the most important contribution to our knowledge of coronary heart disease in recent years was the detailed correlation by Blumgart and his associates (9) of the clinical manifestations of the disease with the pathologic findings in the heart. Complete occlusion of one or more of the major coronary arteries was found in all cases of uncomplicated angina pectoris. In some instances an old area of myocardial infarction was present, but in others there was no such change. In the latter, the occluding thrombi must have developed so gradually that there was time for the establishment of a collateral circulation sufficient to prevent infarction.

DIAGNOSIS.—Angina pectoris has but one pathognomonic feature, and that is paroxysmal pain induced by the factors enumerated. The attacks may be accompanied by other symptoms, but these are of secondary importance and are not necessary for diagnosis. Dyspnea, palpitation, and abnormal sweating are infrequent, and lightheadedness and syncope are rare. A sense of impending death is seldom reported, but many patients acknowledge that there is something about the pain in addition to its severity which forces them to stop. Although objective tests may at times be necessary to eliminate doubt in atypical cases, the diagnosis of angina pectoris rests primarily on an accurate clinical history and its proper interpretation. The pain typically originates in the retrosternal area and most commonly in the middle or upper third. When induced by exertion, it usually is mild at the beginning and then rapidly becomes so severe that the patient is quickly forced to

cease all activity. Rest, as a rule, gives relief within one to five minutes, and nitroglycerin almost always shortens the duration of symptoms still further. Rather than actual pain, many persons describe their discomfort as a sense of constriction, tightness, gas, choking, burning, pressure, aching, heaviness, or fulness. The distress may be accompanied by a desire to belch. In these instances the patient often attributes his symptoms to indigestion rather than to exertion and may be of the opinion that relief depends more on getting rid of a small amount of gas than on rest.

Although the pain of angina pectoris originates characteristically in the substernal area, it arises in other locations in nearly one fourth of all cases. Common atypical sites of origin include the precordium, the right or left infraclavicular region, various parts of one or both upper extremities, the epigastrium, throat, jaws, and upper part of the back. The pain in these areas usually is described as dull, aching, boring, burning, or constricting in quality. There is often prompt radiation to the substernal region, and this is of help in diagnosis. If such radiation does not occur the distress may be wrongly interpreted unless careful inquiry is made concerning the relationship to exertion or emotion and the relief afforded by rest. A therapeutic trial with nitroglycerin may help to clarify the diagnosis.

In typical cases, the pain may or may not radiate beyond its retrosternal site of origin. When radiation occurs, the area most commonly involved is the inner aspect of the left arm down approximately to the level of the elbow. Not infrequently, however, the discomfort extends along the ulnar aspect of the forearm to the wrist or to the tips of the fingers, where it may be described as a feeling of numbness. Occasionally the upper arm is not involved, and the referred pain is localized to a narrow, bandlike zone at the wrist. In place of radiation to the left arm, or along with it, there may be spread to the neck, one or both jaws, the right arm and forearm, the mid-dorsal or left scapular region, or the epigastrium. It should be emphasized that although radiation of the pain is of help in recognizing angina pectoris, it is not essential for diagnosis.

Physical examination of persons who have angina pectoris reveals no characteristic changes either during the attacks or in the

intervals between them. When there is an opportunity to observe an actual seizure, the fixed immobility of the patient during the period of pain and his evident relief as the distress subsides may be striking features.

About one half of all patients who have angina pectoris have a normal electrocardiogram. When no electrocardiographic abnormalities are present and doubt exists as to the diagnosis because of atypical features or the inability of the patient to describe his attacks clearly, the two-step exercise test or the anoxemia test may give helpful information. A positive result can be expected, however, in not more than 60 per cent of all cases in which the control record is normal. The changes induced by exercise or anoxia that are considered to have diagnostic significance are depression of the RS-T segment of at least 1.5 mm. in one or more limb leads or 2 mm. in lead V_4, depression of the RS-T segments in the three standard limb leads and lead V_4 to give an arithmetical sum of 3 mm. or more, development of a typical pattern of acute myocardial infarction or bundle-branch block, or a change in the sign of the T wave except when it occurs in lead III alone. The exercise test has certain advantages over the anoxemia test in the matter of simplicity and safety. Neither should be employed in the presence of congestive heart failure, and both are also contraindicated if myocardial infarction is known to have occurred within the preceding three months or if the control electrocardiogram shows evidence of recent myocardial infarction. Digitalis may cause a false positive response to both tests, and the tests therefore should not be employed if the patient has received the drug during the preceding two weeks.

DIFFERENTIAL DIAGNOSIS.—There are several conditions which cause pain similar to that of angina pectoris. Among these are esophageal hiatus hernia, cardiospasm or spasm of the esophagus, and osteoarthritis of the upper dorsal spine. Pain due to any of these conditions may be situated in the retrosternal area but almost always can be differentiated from the pain of angina pectoris on the basis of differences in the precipitating factors, duration, and the measures which give relief. The pain of cardiospasm or esophagospasm is not related to physical exertion but may be induced by excitement or rapid eating. The discomfort usually lasts longer

than that of angina pectoris. Nitroglycerin may give prompt relief. Pain resulting from esophageal hiatus hernia may be brought on by a large meal or by bending sharply forward, as in tying one's shoestrings. In addition, it often occurs while the patient is recumbent. A moderate or severe anemia is present at times due to loss of blood from the congested mucosa of the herniated portion of the stomach or from a peptic ulcer in that area. This is an important feature because, in patients who have asymptomatic coronary atherosclerosis, the development of anemia from any cause may result in the appearance of typical attacks of angina pectoris. An esophageal hiatus hernia may therefore be the indirect cause of angina, and correction of the anemia may restore the exercise capacity to normal. Osteoarthritis of the dorsal spine occasionally causes pain in the anterior chest with little or no accompanying discomfort in the back. In contrast to angina pectoris, the pain is induced by use of the arms, raising the shoulder, twisting or bending, or turning over in bed. Walking may fail to cause symptoms, and nitroglycerin does not give relief.

The number of cases of angina pectoris which are not correctly recognized is far exceeded by the number in which symptoms not related to the heart are wrongly attributed to coronary insufficiency. The usual cause of the latter type of mistake is incorrect interpretation of the sticking or aching precordial pain encountered so frequently in neurocirculatory asthenia and states of anxiety, fatigue, or nervous tension. The pain in these conditions is not retrosternal in location and does not radiate to that area. At times, however, it spreads upward toward the left shoulder and even down the left arm, usually along the lateral aspect. The sharp or sticking variety of pain may be of no more than momentary duration, but the dull or aching type and that which is described as a sense of heaviness frequently lasts for hours at a time. The discomfort is not induced by physical activity but may develop after a period of exertion. Rest and nitroglycerin fail to give prompt relief. Misinterpretation of the complaint is the most common cause of iatrogenic heart disease, and the principal reason for error appears to be failure to appreciate the difference in significance between precordial and retrosternal pain. The pain of angina pectoris is occasionally precordial in origin, but in those cases there

almost always is an immediate spread to the retrosternal area.

TREATMENT.—The most important single measure in the treatment of angina pectoris consists of a detailed explanation to the patient of the cause and mechanism of his symptoms. Because there is no statistical evidence that the prognosis of the syndrome is affected significantly by drug therapy, chief reliance must be placed on having a patient fully informed as to the nature of his problem. The importance of avoiding the attacks must be stressed, but at the same time the person should be given reasonable assurance of his relative safety so long as he remains free from pain. Mention should be made of the possibility that, with time, an effective collateral circulation will develop and bring with it a considerable improvement in exercise tolerance. A discussion along these lines often greatly reduces the patient's anxiety and apprehension, and this in turn may decrease the frequency of the attacks.

As a part of the instructions, emphasis is placed on the necessity for doing everything slowly and for avoiding heavy lifting, sudden straining, unaccustomed physical activities, and emotional upsets of all kinds. Usually a patient soon learns what activities and emotional states are liable to induce a seizure, and he should be urged to regulate his life so as to eliminate these as completely as possible. There are several conditions which exert an important effect on the ease with which the attacks occur, and these should be discussed thoroughly. In most persons, seizures are induced by less exertion soon after eating than at other times, and because of this a rest period of 30–45 minutes after every meal is advisable. Resting in a chair is preferable to lying down. The three daily meals should be relatively small and approximately equal in size. Overeating must be avoided at all times because an excessively large meal may cause an attack in the absence of all other precipitating factors. Overweight individuals should be placed on a reducing diet, for the loss of excess weight often results in definite improvement in exercise tolerance. Exposure to cold weather frequently increases the ease with which anginal attacks occur. The patient, therefore, should be advised to dress warmly during the winter months and to use mittens or gloves. Walking against a wind or through snow places a considerably added load on the heart and should be avoided as far as possible. Snow shoveling must be pro-

hibited. Whenever the patient's financial circumstances permit it, he should spend the most inclement months of the year in the South.

Controversy continues as to whether or not persons who have angina pectoris should be allowed to smoke. In patients who have been heavy smokers, a decided diminution in the frequency of attacks and the ease with which they are induced may follow the giving up of tobacco. Because of this it appears best to prohibit smoking in all individuals who have angina pectoris, with the possible exception of those past 65.

Every person who has angina pectoris should be instructed to stop all activity and stand still immediately upon the first appearance of symptoms. To reduce the gait without stopping is not enough. In certain instances the initial attacks of angina are extremely severe, and in others there is an abrupt increase in the frequency and severity of the seizures after a variable length of time. Both of these situations are often due to gradual thrombotic occlusion of a coronary vessel. In order to reduce the chance that this may result in acute myocardial infarction, the work of the heart should be reduced to a minimum by a period of strict rest.

Drugs employed in the treatment of angina pectoris fall into two classes. The first consists of preparations for terminating the attacks, and in this group the two agents of established value are nitroglycerin and amyl nitrite. Nitroglycerin is to be preferred, for it is just as effective as amyl nitrite, has a somewhat longer period of action, is less unpleasant and more convenient to use, and more economical. The dose customarily prescribed is larger than is necessary. Tablets containing 0.3 mg. (1/200 gr.) usually are just as effective as larger amounts and are less likely to cause undesirable side effects. Every person who has angina pectoris should be supplied with a number of the tablets with instructions to use one sublingually whenever an attack is not relieved within one minute by rest. The repeated use of nitroglycerin is not harmful, but this does not excuse a person from exercising every possible precaution to avoid the seizures.

Nitroglycerin also is employed in a prophylactic manner. Certain patients are forced by the nature of their occupation to carry out activities each day which regularly induce an attack, and these

seizures often can be prevented by taking a tablet of the drug shortly before the unavoidable exertion. The use of nitroglycerin in this manner often enables a patient to get along comfortably and remain self-supporting for a long time. It does not relieve him, however, of the responsibility for avoiding unnecessary activities which may bring on an attack.

The second group of drugs employed in the management of angina pectoris is composed of preparations designed to improve the exercise capacity of the patient and reduce the frequency of the attacks. The drugs in most common use are purine derivatives, such as theobromine and sodium acetate, theobromine and calcium salicylate, and aminophylline. Other preparations include papaverine, Pavril, khellin, heparin, pentaerythratol tetranitrate (Peritrate), alcohol, and testosterone propionate. There is very little objective evidence that any of these are of clinical value. Peritrate partially prevents the electrocardiographic abnormalities induced by exercise tests, but this effect is rarely accompanied by a measurable decrease in the frequency or severity of clinical attacks of angina pectoris. Alcohol, after a thorough trial, has been almost entirely discarded because of the realization that its occasional helpfulness was due to a reduction of the patient's anxiety and apprehension, an effect which can be secured just as readily by mild sedatives. Heparin is of no value, and its use is not without danger. Certain of the preparations belonging to the purine group do seem at times to be of some help. The apparent benefit, however, is observed only in patients who have been fully instructed regarding the avoidance of factors that may precipitate a seizure. Without attention to these restrictions, there is seldom a reduction in the frequency or severity of the attacks. The action of the drugs, therefore, may be entirely psychologic. Even so, the psychologic aspects of the treatment of angina pectoris are of great importance. To dismiss a patient with nitroglycerin as his only medication or to prescribe an additional preparation which he recognizes as a sedative, may immediately convince him that his situation is hopeless. It therefore appears best to give every patient with angina pectoris a trial on one or more of the purine derivatives and to continue treatment indefinitely in those who seem to be benefited. Riseman, Steinberg and Altman (10) recently reported that qui-

nine, quinidine, and certain other cinchona alkaloids are beneficial in some but not all patients, the effectiveness of the drugs being due, at least in part, to a vasodilator action.

Digitalis has no place in the management of uncomplicated angina pectoris. The development of dyspnea on exertion or the occurrence of congestive heart failure is, however, an indication for its use.

Angina decubitus is more common than generally realized and is a difficult therapeutic problem. Improvement occasionally results from a period of strict rest and a program of dehydration by means of a low-sodium diet and the administration of mercurial diuretics.

A number of patients who have angina pectoris become unable to perform activities of any kind without experiencing pain. Formerly, it was in these that surgical measures such as paravertebral injections of alcohol or removal of the upper four or five thoracic sympathetic ganglia were at times carried out. Today, the surgical treatment of angina pectoris is limited to certain procedures designed to augment coronary blood flow. None of the operations can be considered beyond the developmental stage, although some appear to have promise. The present treatment of choice for intractable angina pectoris consists of inducing hypothyroidism by means of radioactive iodine. The value of this method has been firmly established by the results obtained in a large number of cases treated in several different clinics (11). Induced hypothyroidism does not, of course, alleviate the underlying coronary atherosclerosis, but it does result in a reduction in the severity and frequency of anginal seizures in approximately 75 per cent of properly selected cases. It has not been established that the patient's life is prolonged. The procedure is employed only in cases that cannot be controlled satisfactorily by the usual measures of treatment. The greatest benefit is obtained in patients whose condition has remained relatively stationary or has progressed only slightly over a period of a year or more. Blumgart (11) advises that the original basal metabolic rate be above −10 per cent and points out that hyperactive, tense patients are particularly favorable candidates. Recent myocardial infarction, angina pectoris of recent onset, and

any evidence of rapidly progressive cardiovascular disease should be considered contraindications.

PROGNOSIS.—The clinical course of angina pectoris varies within wide limits. An occasional patient experiences a few mild attacks and then remains free from symptoms for months or years. Others have frequent and increasingly severe paroxysms terminating within a short time in sudden death. In many, the frequency of the seizures and the ease with which they are brought on fluctuate within wide limits from time to time. Changes in the general health of the individual, variations in the amount of stress in his life, and seasonal changes in the weather account for some of these fluctuations. Others apparently are to be explained by alterations in the relative effectiveness of the collateral coronary circulation to regions of myocardial anoxia. The development of adequate intercoronary anastomoses may afford freedom from attacks for long periods, and an occasional patient is even permanently relieved.

The prognosis of the individual patient with angina pectoris is always uncertain, for there is no reliable guide for predicting the course of events. Severe and prolonged attacks which are induced by very little activity or excitement, or occur at rest, indicate a limited expectancy. Mild seizures which are experienced at infrequent intervals and are brought on only by unusual exertion imply a reasonably good outlook but do not justify too great optimism. Block and his associates (12) studied 6,882 cases of angina pectoris and reported a mortality rate of 15 per cent during the first year after diagnosis and approximately 9 per cent annually among the survivors in each subsequent year. The rate was greater for men than for women and was increased by the presence of cardiac hypertrophy, congestive heart failure, hypertension, electrocardiographic abnormalities and previous myocardial infarction. In the absence of these factors, the average patient suffering from angina pectoris has, after the first year, a better than 90 per cent chance of surviving more than one additional year.

ACUTE MYOCARDIAL INFARCTION

Because the clinical picture of acute myocardial infarction is too well known to warrant detailed description at this time, this

discussion will be devoted mainly to a consideration of diagnosis and treatment. It is appropriate to point out at the beginning that myocardial infarction and coronary thrombosis are not synonymous terms. Blumgart (9) demonstrated in his observations on patients with angina pectoris that coronary thrombosis may fail to cause myocardial infarction. Furthermore, although acute coronary thrombosis is the most common cause of myocardial infarction, infarction not infrequently occurs in the entire absence of coronary occlusion. In some series of acute infarction, instances of this kind have comprised 30 per cent of autopsied cases. When infarction occurs in the absence of coronary artery occlusion, the cause is some other factor which results in severe and prolonged myocardial anoxia. This may be an abrupt and prolonged reduction in coronary blood flow secondary to hemorrhage, vasovagal syncope, traumatic or surgical shock, or a fall in arterial pressure due to spinal anesthesia. In other cases, paroxysmal tachycardia or a sudden increase in the demands on the heart by exertion or emotion may be responsible. Myocardial infarction can be diagnosed with great accuracy, but often one can only speculate as to whether the condition has resulted from acute coronary thrombosis or from prolonged myocardial anoxia without coronary occlusion. Attacks of infarction which develop in the absence of apparent precipitating factors or while the patient is asleep are usually due to acute coronary thrombosis.

There has been considerable difference of opinion as to the frequency with which capillary hemorrhage into an atheromatous plaque is the factor directly responsible for the occurrence of acute occlusion of a coronary artery. Some have expressed the belief that this is the most common immediate antecedent of acute coronary thrombosis, but others have not been in agreement. The recent study of Drury (13) does much to resolve the issue. He points out that although intimal hemorrhage is a common complication of coronary atherosclerosis, the blood is seldom of capillary origin. Instead, it usually comes from the lumen of the artery through an area of rupture or abnormal permeability of the endothelium secondary to underlying atheromatous necrosis. The area of rupture or necrosis of the endothelium, in turn, affords an excellent site for the evolution of a thrombus. In other words, endothelial rupture or

necrosis is the primary cause of both acute coronary thrombosis and intimal hemorrhage, but the two latter conditions are otherwise unrelated. Drury believes that capillary hemorrhage into an atheromatous plaque is of little clinical importance and that the limited possibility of its occurrence does not contraindicate the use of anticoagulant drugs.

DIAGNOSIS.—The pain of acute myocardial infarction is similar in location and radiation to that of angina pectoris but, with exceptions, is of greater severity. It usually lasts for more than one-half hour and often for several hours, depending on the size of the infarct, the patient's tolerance to pain, the degree of accompanying shock, and the promptness with which treatment is started. Nitroglycerin is without effect, and morphine gives only gradual relief. These features distinguish myocardial infarction from angina pectoris but do not differentiate it from the syndrome of coronary failure, which is discussed later. Confirmation of a clinical diagnosis of acute infarction rests entirely on the development of evidence of acute necrosis of myocardial tissue. Fever, leukocytosis, elevation of the erythrocyte sedimentation rate, a pericardial friction rub, and characteristic changes in the electrocardiogram are the chief manifestations of this process, and one or more of them must appear subsequent to the onset of symptoms before the diagnosis can be considered established. Fever and leukocytosis usually develop within 24–48 hours after the onset of pain, and the erythrocyte sedimentation rate becomes accelerated within the first three or four days. A pericardial friction rub is detected in approximately 10 per cent of the cases and may last for a few days or for only a few hours. The electrocardiogram shows diagnostic changes in practically every patient if records are made at daily intervals and if multiple precordial leads are used in addition to the standard and unipolar limb leads. Occasionally a high lateral or a small posterior infarct may produce no more than suspicious changes in the conventional leads, and an electrocardiographic diagnosis requires further exploration over the left upper chest, left axilla and left side of the back.

Although pain is the predominant symptom in most cases of acute infarction, there are a few instances in which it is entirely absent. Traumatic or postoperative shock, pre-existing congestive

heart failure, or depression of the sensorium by drugs or toxic states may be responsible for failure of pain to occur, but occasionally there is no apparent cause. Painless infarction, however, is not "silent," and the term "silent infarction" should be discarded. Usually in painless cases, the onset of the attack is signalized by the abrupt development of dyspnea which may or may not be accompanied by objective evidence of acute left ventricular failure. In other instances, the initial symptom is sudden weakness, syncope, or collapse.

DIFFERENTIAL DIAGNOSIS.—In the literature on myocardial infarction, attention has been directed repeatedly to the fact that the pain may simulate that of biliary colic or acute surgical conditions in the upper abdomen. Actually, there are relatively few cases in which the similarity is so close that a real danger of erroneous diagnosis exists after a careful history and physical examination. When the pain of acute infarction originates in the upper abdomen, there almost always is prompt radiation to the retrosternal area or at least accompanying distress in that region. This feature or the presence of cardiac abnormalities such as gallop rhythm and heart sounds of poor quality should lead to thorough electrocardiographic study.

Three conditions which may present a more difficult problem in differential diagnosis are acute nonspecific pericarditis, pulmonary embolism, and dissecting aneurysm of the aorta. The pain in acute benign pericarditis is usually substernal but is not accompanied by symptoms of shock. It is increased by deep breathing but not by walking. A pericardial friction rub is present from the beginning of the illness, in contrast to its appearance after an interval of days in myocardial infarction. In acute pericarditis, also, fever, leukocytosis, and elevation of the sedimentation rate are present at the onset and may even antedate the pain. In many cases there is a history of a preceding infection in the upper respiratory tract. The electrocardiogram commonly shows changes which may or may not be diagnostic of pericarditis but are readily distinguishable from those of acute infarction.

Embolic occlusion of the pulmonary artery or one of its larger branches may result in sudden death or cause the abrupt onset of severe dyspnea accompanied by cyanosis, retrosternal pain or op-

pression, and the rapid development of a state of shock. If the condition is not promptly fatal, fever and leukocytosis usually appear within 24 hours. The sudden increase in pulmonary vascular resistance frequently results in a palpable pulsation in the left second intercostal space and accentuation of the pulmonary second sound. Right ventricular dilatation and failure often follow, with elevation of the peripheral venous pressure. Gallop rhythm may be present over the pulmonary area, and at times a friction rub is heard in this region. The electrocardiogram may show temporary changes consisting of a deep S_1, depression of the RS-T segment in lead II, and prominent Q waves and inverted T waves in lead III. In other instances, there is transient right bundle-branch block.

Although dissecting aneurysm of the aorta in its fully developed stage does not present a difficult problem in diagnosis, the early symptoms may be highly suggestive of acute myocardial infarction. The pain often originates in the anterior chest but is usually abrupt in onset, in contrast to its more gradual evolution in acute infarction. It lasts for 48 hours or longer and often persists in greater or lesser degree until death occurs. Repeated injections of morphine afford only partial and gradual relief. The pain may radiate to the back, arms, abdomen, or legs, and there may be symptoms and signs of impairment of the arterial circulation to the brain or one or more extremities. Injury to the nutrient arteries of the spinal cord may result in paresthesia or paralysis of the legs. Hypertension is usually present and is often maintained throughout the illness. The intensity of the heart sounds is not diminished, and, except in the rare instances where coronary blood flow is interfered with by proximal dissection of the aneurysm, the electrocardiogram does not show the changes of myocardial infarction.

TREATMENT.—The treatment of acute myocardial infarction consists of measures to relieve the pain and combat complications, the administration of anticoagulant drugs whenever feasible, an adequate period of rest, and the management of sequelae. For the relief of pain, morphine sulfate or meperidine hydrochloride remain the drugs of choice. When morphine is employed, the initial dose is usually 15 mg. (¼ gr.) hypodermically, but whenever the pain is unusually severe, one should not hesitate to administer 30

mg. (½ gr.). If the pain is extreme, 15 mg. may be given by intravenous injection. Subsequent doses of 15 mg. should be given subcutaneously at intervals of one-half hour or so if the distress continues unabated, but the total amount administered should not exceed 60 mg. (1 gr.), and the drug should not be employed after the pain begins to subside.

The patient should be placed in bed as soon as possible after the onset of symptoms, preferably with the headposts of the bed elevated on 6–9 in. blocks, and should not be disturbed by frequent examinations. In the more severe attacks which are accompanied by prolonged pain, cyanosis, and intense dyspnea, oxygen should be given as promptly as possible. This often reduces the cyanosis and dyspnea and may also lessen the intensity and shorten the duration of the pain.

The prognosis of the immediate illness in acute myocardial infarction is determined mainly by the size of the infarcted area and by whether certain complications develop. The principal complications are shock, acute left ventricular failure, congestive heart failure, disturbances of cardiac rhythm, thromboembolism, rupture of the ventricle, perforation of the interventricular septum, and rupture of a papillary muscle. Because of their importance, it is essential that everything possible be done to prevent those of these conditions which are preventable and to institute prompt treatment of those for which therapeutic measures are available.

A shocklike state of mild to severe degree occurs in 50 per cent or more of all cases of acute infarction. Cold, clammy perspiration, weakness, faintness, and nausea are common, and there may be grayish pallor, cyanosis, vasomotor collapse, and loss of consciousness. Opinions differ as to whether the syndrome is due chiefly to an abrupt reduction in cardiac output or to reflex peripheral circulatory failure with impairment of venous return to the heart. The available evidence indicates that both factors are present in different degrees in different cases. Fink and his associates (14) believe that patients with shock due to myocardial infarction are divisible into two groups on the basis of the height of the venous pressure. In those with low venous pressure, shock is due primarily, in their opinion, to loss of peripheral vascular tone and diminished return of blood to the heart. In patients with high venous pressure,

on the other hand, the chief cause of shock is considered to be acute heart failure of such severity that the cardiac output is insufficient to maintain adequate arterial pressure levels. The first form may progress to the second.

The most important recent development in the treatment of shock due to myocardial infarction has been the demonstration of the beneficial effect of vasoconstrictor agents. There is now quite general agreement that a preparation of this type should be administered whenever shock develops or the arterial blood pressure falls to approximately 80 mm. Hg. The drug most widely used is nor-epinephrine (Levophed) diluted in 1,000 cc. of 5 per cent glucose in distilled water and administered by continuous slow intravenous drip in amounts sufficient to maintain a systolic pressure of 100 mm. Hg or somewhat higher. Mild shock usually responds promptly, and occasionally even severe cases are corrected. In the few studies, however, in which the effect of vasoconstrictor drugs has been considered separately in mild and severe shock, the mortality rate in severe shock does not appear to have been improved significantly.

When vasoconstrictor preparations fail to help, intravenous administration of 250–500 cc. of plasma or whole blood, or intra-arterial transfusion of whole blood, may be beneficial. Fink and his associates (14) believe that these measures, as well as vasoconstrictor agents, are of value only in cases in which the venous pressure is low. When the venous pressure is high, myocardial failure is the principal cause of the shock, and the essential measure in treatment is the administration of digitalis.

Acute left ventricular failure often accompanies the onset of myocardial infarction or appears within a few days. There are intense dyspnea, orthopnea, frequent coughing, and a sense of suffocation. The breathing frequently becomes asthmatic, and if the attack is of sufficient severity, acute pulmonary edema may supervene. The symptoms may or may not be accompanied by shock. Treatment consists of the intravenous administration of aminophylline and prompt digitalization. Morphine may be necessary for relief of dyspnea, and oxygen should be given in the severer attacks. When these measures fail to help sufficiently, and if shock is not present, the removal of 250–500 cc. of blood by venesection

or the application of tourniquets to the four extremities may be strikingly beneficial. These measures should not be employed, however, in the presence of shock.

Left ventricular failure of milder degree probably is much more common during the early period after myocardial infarction than is generally realized. If not detected and treated, the condition may have an important effect on the mortality rate. Because of this, careful auscultation of the lung bases should be carried out at least twice a day during the first few days of the illness, and digitalis should be administered on the first appearance of râles. The sodium content of the diet should be restricted, and one of the mercurial diuretics should be given at intervals of two or three days until the drug no longer causes increased diuresis. In the past, far too much emphasis has been placed on theoretical objections to the use of digitalis in acute myocardial infarction. These objections have not been substantiated by clinical experience, and there is now general agreement that left ventricular failure of all degrees is an indication for the use of the drug. Digitalization is usually accomplished by the oral route, but when acute pulmonary edema develops, a suitable preparation, such as lanatoside C, should be given in proper amounts by intravenous injection. It is essential, of course, to ascertain beforehand that the latter patients have not received digitalis during the preceding two weeks.

Congestive myocardial failure of the combined right and left ventricular type seldom occurs immediately after acute infarction but not infrequently develops within a few days or weeks. This is especially liable to be the case if the early stages of preceding left ventricular failure have been overlooked. The clinical manifestations and treatment do not differ from those of decompensation due to other forms of heart disease.

Abnormalities of cardiac rhythm are common during the first few days after the onset of myocardial infarction, the most frequently observed being premature beats, auricular fibrillation, and auriculoventricular block. Premature beats, usually of ventricular origin, occur in many patients, and if few in number, they are of no importance. When more numerous, they may be the precursor of ventricular paroxysmal tachycardia which in turn may be responsible for the development of acute pulmonary edema, con-

gestive heart failure, peripheral circulatory collapse, or fatal ventricular fibrillation. Auricular fibrillation complicating myocardial infarction usually is of the paroxysmal variety and lasts, as a rule, for only a few hours or days. Auriculoventricular block may be of any degree from simple prolongation of auriculoventricular conduction time to complete dissociation of the auricles and ventricles. Complete auriculoventricular dissociation and the higher grades of partial block may be responsible for Adams-Stokes attacks.

Frequent premature beats are treated by the oral administration of 0.2–0.4 Gm. of quinidine or 0.25–0.5 Gm. of Pronestyl every four to six hours. The development of ventricular tachycardia calls for the use of larger amounts of either preparation at more frequent intervals or, if the patient is critically ill, for parenteral administration. Auricular fibrillation is treated by rapid digitalization, usually by the oral route. The Adams-Stokes syndrome, except in rare instances, is of such short duration that no treatment is required. The attacks are likely to recur, however, and for their prevention the most helpful drug is isopropyl nor-epinephrine (Isuprel) administered sublingually in doses of 15 mg. three or four times a day (15).

The data accumulated by the Committee on Anticoagulants of the American Heart Association conclusively demonstrate that anticoagulant therapy results in an important reduction in the frequency of thromboembolic complications and in the mortality rate of acute myocardial infarction (16). The Committee therefore recommends the use of anticoagulants in all cases of infarction except when their employment is contraindicated by the presence of hepatic or renal insufficiency or a blood dyscrasia with hemorrhagic tendencies, or when facilities are not available for making reliable measurements of the prothrombin time of the blood. These recommendations probably are being followed today in the majority of medical centers, but during the past three years doubt has been expressed with increasing force about the need for anticoagulant therapy in every case of infarction. Russek and his colleagues (17), and others, have published thought-provoking studies. In their opinion, treatment of this kind is not necessary in "good risk" cases. These are cases in which there has not been previous myo-

cardial infarction or pulmonary embolism, and in which the present illness is not attended by prolonged pain, severe or persistent shock, or congestive heart failure. Enlargement of the heart, gallop rhythm, important disturbances of heart rhythm, intraventricular block, diabetic acidosis, obesity, varicosities in the lower extremities, and thrombophlebitis or other states predisposing to thrombosis should not be present. In 204 patients who met these qualifications and were treated without anticoagulants by Russek and his group, the mortality rate was only 2.45 per cent. When the fatalities which could not have been prevented by Dicumarol were eliminated, the rate was still further reduced to 0.98 per cent. The incidence of thromboembolism was less than 1 per cent. These figures certainly call for further studies of a similar nature. Until they have been corroborated on an extensive scale, however, it appears best to continue the routine administration of anticoagulants whenever a reliable laboratory is available and there are no contraindications for use of the drugs. The main problem is to be certain that "good risk" cases can be reliably identified.

The prothrombin clotting time is measured before the initial dose of anticoagulant is given and on each day thereafter. Dicumarol remains the preparation of choice. Tromexan has largely done away with the need for giving heparin during the first 24–48 hours of therapy. Because it is difficult to maintain a constant therapeutic prolongation of the prothrombin time with this drug alone, it has become common practice to administer a dose of 1,200–1,800 mg. at the same time as the first dose of Dicumarol (300 mg.). Tromexan is not repeated, but on subsequent days Dicumarol is given in amounts sufficient to maintain the prothrombin time between 25 and 30 seconds. Anticoagulant therapy is continued for a minimum of three weeks.

Mural thrombi are found within the left ventricle in about 50 per cent of all patients with myocardial infarction examined at autopsy and are a common source of emboli to the brain and peripheral arterial circulation. Not every instance of occlusion of a peripheral artery after myocardial infarction, however, is due to embolic obstruction. Local thrombus formation is responsible in a considerable number of cases. There is evidence that the incidence of intracardiac thrombosis is reduced by anticoagulant therapy.

One of the most common and serious thromboembolic complications of myocardial infarction is pulmonary embolism. The emboli usually arise from thrombi in the veins of the legs, although occasionally, when infarction involves the interventricular septum or there has been prolonged congestive failure, they may originate from mural thrombi in the right ventricle. There are two measures, in addition to the use of anticoagulants, that may help prevent pulmonary embolism by reducing the incidence of phlebothrombosis in the lower extremities. These are the routine use of elastic stockings and a program of early active and passive movements of the legs.

In approximately 10 per cent of all patients who die within the first two weeks after acute myocardial infarction, death is due to one of three complications. These are rupture of the ventricle, perforation of the interventricular septum, and rupture of a papillary muscle. In rupture of the ventricle, death almost always is sudden, but in exceptional instances when the tear is minute it may be delayed for several hours. Two factors that appear to favor the occurrence of rupture are continued physical activity on the part of the patient and the persistence of hypertension after infarction. However, not every case of hematopericardium complicating acute infarction is due to rupture of the ventricle. Gross extravasation of blood may occur from an area of fibrinous pericarditis overlying a transmural infarct or even from areas of pericarditis at a distance from the infarct (18). Although this has been observed in patients who have not had anticoagulants, it is more likely to be encountered in those receiving these drugs. The development of any evidence of pericardial effusion after acute infarction should raise the suspicion of hematopericardium and lead to the prompt use of anticoagulant-neutralizing measures. Perforation of the interventricular septum is much less common than rupture of the ventricle, and patients at times live for weeks or months after its occurrence. Its development is signalized by the sudden onset of severe dyspnea, with or without substernal pain, and the appearance of a loud, harsh systolic murmur along the lower left sternal border. The murmur is usually accompanied by a systolic thrill. Symptoms of shock and progressive right ventricular failure complete the clinical picture. Rupture of a papillary muscle is a rare complication

of infarction which in most instances proves fatal within a few hours. Its characteristic features are an abrupt onset of dyspnea and intractable pulmonary edema and the appearance of a loud systolic murmur at the cardiac apex. There is no thrill. The symptoms and signs are due to the sudden development of free mitral regurgitation in the presence of recent severe damage to the left ventricular myocardium.

A period of strict rest is an essential part of the management of every case of acute myocardial infarction. One of the most significant advances in treatment during the past few years, however, has resulted from a re-definition of the term "strict rest." Evidence has accumulated that the former practice of prohibiting all active movements, insisting on the use of a bedpan rather than a commode at the bedside, and enforcing a period of six to eight weeks' rest in bed before allowing the patient to sit up in a chair are not prerequisites for the successful management of acute infarction. Too often in the past, subsequent reassurance by the physician and the patient's friends has not been able to neutralize the sense of insecurity generated by such a program, and needless permanent invalidism has resulted. Levine and Lown (19), and others, have demonstrated that after the period of shock is past, and in the absence of great debility or a cerebral vascular accident, the patient may safely be permitted to sit in a chair for as long each day as he desires. He should be helped in and out of bed, however, and should be allowed no other privileges except for the use of a commode at the bedside. The length of time this program is carried out before allowing him to walk again is determined by the severity of the attack. Histologic studies indicate that small infarcts are almost completely healed after five weeks and large ones after two months. Most patients can be permitted to take a few steps to the bathroom at the end of three weeks and can be granted gradually increasing activity after six weeks. In the absence of angina pectoris and myocardial insufficiency, return to some form of work is usually permissible at the end of three months. The degree of activity allowed should be governed principally by the presence or absence of symptoms referable to the heart and not by the size of the heart or the findings in the electrocardiogram.

The most common sequelae of acute myocardial infarction are

angina pectoris, a permanent reduction in myocardial reserve, anxiety states focused on the heart, periarthritis of the shoulder with or without the shoulder-hand syndrome, deposition of calcium in the scar of the infarct, and aneurysm of the ventricle. The clinical significance of most of these conditions is well recognized and will not be discussed. Periarthritis of the shoulder deserves a few words because the patient often assumes that the pain in the shoulder is indicative of some further injury to the heart. The condition occurs in approximately 15 per cent of all patients with myocardial infarction and usually develops within a few weeks after the onset of the attack. In about one third of the cases there is an associated painful disability of the hand and wrist to complete the picture of the shoulder-hand syndrome. The primary cause of the condition is not known, but disuse of the shoulder and protective tension of the shoulder muscles appear to be at least important contributory factors. It is for this reason that active movements of the arms and shoulders are recommended early in the treatment of patients with myocardial infarction. When symptoms develop in spite of these measures, mild cases may require only analgesics, the local application of heat, and massage followed by passive and active movements. Intermittent traction to the arm may be necessary in more severe cases. Injection of procaine hydrochloride into the stellate ganglion often results in prompt initiation of improvement, and cortisone or corticotropin for several days may have a similar effect. Local injections of hydrocortisone also have been reported to be beneficial.

Aneurysm of the left ventricle is found at postmortem examination in 10–20 per cent of all cases of myocardial infarction in which the patient does not die soon after the onset of the attack. The noncontractile tissue of a fresh infarct is subjected to the force of intraventricular pressure with each systolic contraction of the heart, and within a few days or weeks a distinct outward bulge may develop. Inadequate rest, the persistence of hypertension, and the presence of valvular disease or malformations of the great vessels appear to favor its development (20). The lesion can be demonstrated in roentgenograms taken at an appropriate angle, and on fluoroscopy one may be able to detect a paradoxical pulsation in the aneurysmal sac. Electrocardiograms may also show persistent

changes of diagnostic significance. Although persons who have an aneurysm of the heart may live for several years, the general prognosis is poor. Intramural thrombosis and thromboembolic accidents are much more common than in patients with infarction but no aneurysm. Seventy-three per cent of the 102 patients studied by Schlichter, Hellerstein, and Katz (20) died within three years after infarction, the principal causes of death being congestive heart failure and recurrent myocardial infarction. It is to be emphasized that once an infarct is completely healed, a ventricular aneurysm is not attended by the danger of rupture.

Prognosis.—Acute myocardial infarction is always a serious condition, and only a guarded prognosis is justified in the early part of the illness. In large series of cases, the mortality rate during the first two months after the onset has ranged from 10 to nearly 25 per cent. Factors which adversely affect the immediate prognosis include shock or pain of long duration, a pronounced and sustained fall in arterial blood pressure, persistent elevation of the heart rate above 100 beats per minute, auriculoventricular or intraventricular block, gallop rhythm, pulses alternans, more than slight enlargement of the heart, and congestive heart failure. In patients who survive the immediate illness, the outlook is better than was indicated by the early statistical studies. This improvement probably is due in large part to the fact that better diagnostic methods have led to the recognition of many mild cases which formerly were overlooked. Cole, Singian and Katz (21) recently published a study of the long-term prognosis after the first attack of infarction. Of 285 patients who survived for more than two months, 67 per cent lived more than five years, 44 per cent more than 10 years, and 10 per cent more than 15 years. At the conclusion of the study, 89 patients were still living, and in these the average survival period was 14 years. The prognosis proved to be better in younger than in older patients and was slightly better for men than for women. The chances for prolonged survival were improved by the absence of hypertension and diabetes mellitus and were diminished by the occurrence of congestive failure during the acute illness. Although shock affected the immediate outlook, it did not influence the long-term survival rate. Pulmonary embolism and gallop rhythm were attended by a poor

prognosis both for the acute illness and for prolonged survival. Patients in whom the onset of symptoms occurred while at rest and those in whom the leukocyte count became greatly elevated had a poorer immediate and long-term prognosis. Anterior infarction had the same survival rate as posterior. Subendocardial infarction had a good outlook, but cardiac arrhythmias and disturbances of the conduction mechanism lessened the chance of prolonged survival. Approximately two thirds of the patients were able to return to moderate or complete activity; one fourth were considerably limited in their activities, and 10 per cent remained bedridden. The ability of the patient to resume activity appeared to be the best index to prognosis after recovery from the first attack of infarction. Of those in this study who were able to return to complete activity, 71 per cent lived over 10 years. The most frequent cause of death following recovery from one infarction was another myocardial infarction, and the second most common cause was congestive heart failure.

Acute Coronary Failure

In 1940, Blumgart and his associates (9) focused attention on a previously neglected form of coronary heart disease characterized by attacks of substernal pain of longer duration than in angina pectoris but not followed by clinical or electrocardiographic evidence of myocardial infarction. The physiologic basis for the pain in this condition is the same as in angina pectoris, namely, a reversible myocardial anoxia. The anoxia lasts longer than in angina pectoris but not long enough to cause myocardial necrosis. The term "coronary failure" was applied to the syndrome. Recognition of the condition is important because, among other considerations, the attacks at times represent the premonitory symptoms of acute infarction. The pain usually lasts for 20 minutes or longer, may be of any intensity from mild to very severe, and at times is accompanied by some respiratory distress, sweating, and weakness. Nitroglycerin usually fails to give more than partial and temporary relief. Fever, leukocytosis, and an elevated sedimentation rate do not occur, and there is no subsequent progressive decline in blood pressure. Electrocardiograms made during the attack may show

changes similar to those which occur in many patients during seizures of angina pectoris. The changes, when present, are of short duration, and subsequent tracings fail to show the serial alterations of acute infarction.

In certain patients, attacks of acute coronary failure are induced by factors which either increase the demands on the heart for work or impair coronary blood flow. Thus, exertion, emotion, sudden exposure to cold, paroxysmal arrhythmia or tachycardia, and hypotensive states due to shock or hemorrhage may be responsible. Autopsy studies in such cases reveal extensive coronary atherosclerosis but no fresh arterial occlusion. In other patients, attacks occur at rest or are precipitated by degrees of exertion or emotion which previously had failed to cause symptoms or had induced only a typical seizure of angina pectoris. The available evidence indicates that in these instances the symptoms are due to partial or complete thrombotic occlusion of a coronary branch. The occlusion, however, does not result in myocardial infarction because coronary artery disease of sufficient degree has been present long enough to result in the development of adequate pathways of collateral circulation. Obstruction of the affected vessel therefore does not interfere with the nutrition of the myocardium to the extent necessary to cause necrosis of tissue, but it does cause a prolonged period of anoxia.

Because acute coronary failure may be the precursor of acute myocardial infarction, the demands on the heart should be reduced to a minimum as quickly as possible. Rest according to the "armchair" schedule is advisable for 10–14 days. In patients in whom the attack can reasonably be presumed to have been due to acute coronary thrombosis, anticoagulants should be administered as a prophylactic measure against propagation of the thrombus.

Congestive Heart Failure

The clinical manifestations and treatment of congestive heart failure due to coronary artery disease do not differ from those of failure due to other forms of heart disease. The condition is a common complication or sequel of acute myocardial infarction, as mentioned earlier, and occurs eventually in about one fourth of

all persons who have angina pectoris. In the latter patients, its development appears to be due to fibrous scars in the myocardium which result from repeated episodes of myocardial ischemia. Myocardial fibrosis and congestive failure may also occur in an occasional patient who has advanced coronary atherosclerosis but has not experienced attacks of cardiac pain. However, the development of cardiac decompensation in an elderly person who does not have hypertension, valvular heart disease, or evidence of occlusive vascular disease in other parts of the body is not sufficient reason for an unqualified diagnosis of coronary heart disease. If the patient has not experienced angina pectoris, acute coronary failure, or acute myocardial infarction, there must at least be electrocardiographic abnormalities which can reasonably be attributed to coronary atherosclerosis. Morgan (22) and others have directed attention to the fact that anatomic and physiologic changes in the heart due to senescence alone may be the sole cause of congestive failure. The same changes may be responsible for cardiac arrhythmias, but whether they can also produce abnormal T waves in the electrocardiogram and auriculoventricular or intraventricular block remains to be demonstrated. At times, senescence of the myocardium appears to be the principal factor which determines the eventual development of cardiac failure in elderly patients with previously asymptomatic hypertensive, valvular, or coronary heart disease. The problem of the senile heart deserves intensive study.

MANAGEMENT OF CORONARY HEART DISEASE IN RELATION TO SURGERY

Although the risk of anesthesia and surgical operations is greater in patients who have coronary heart disease than in normal persons, the difference is not forbidding and should not be magnified beyond its true proportions. The increased risk is due to the fact that in patients who have a history of angina pectoris, acute coronary failure, or myocardial infarction, there is heightened susceptibility of the heart to anoxia and increased carbon dioxide tension. If these are avoided by skilful anesthesia, minimizing of blood loss, and the prevention of hypotension during and after operation, surgical mortality is only slightly greater than in normal

persons. Anoxia, carbon dioxide accumulation in the anesthesia circuit, or a reduction in coronary blood flow, on the other hand, may cause coronary failure, acute nonthrombotic myocardial infarction, serious arrhythmias, or cardiac arrest.

In order to obtain the minimal surgical mortality and morbidity rates in coronary heart disease, certain other precautions must be observed. Congestive heart failure, when present, should be treated as thoroughly as possible before operation. The ventricular rate in auricular fibrillation or auricular flutter should be controlled by adequate digitalization. Operation should be postponed, if at all possible, for at least three months after acute myocardial infarction and for at least two weeks after an attack of coronary failure. The electrocardiogram should be repeated on the morning or afternoon before surgery to exclude recent infarction. The presence of coronary heart disease is seldom of more than secondary importance in determining the agent to be used for general anesthesia. Instead, the patient's general condition and the type of operation are the deciding factors. If spinal anesthesia is used, however, extra care must be employed to avoid a drop in arterial pressure during the operation and the postoperative period. Neo-synephrine can be administered for this purpose.

One feature of the postoperative management of patients who have coronary heart disease deserves emphasis. This has to do with the administration of fluids by intravenous injection. All preparations which contain sodium, including whole blood and plasma, should be avoided unless their use is specifically indicated. When fluids must be given intravenously, the solution should consist only of 5 per cent glucose in distilled water whenever possible. The administration of large amounts of sodium-containing fluids to patients who have coronary heart disease may be directly responsible for the development of pulmonary edema and other features of congestive heart failure even though there may have been no symptoms of myocardial insufficiency before operation. The danger is, of course, particularly great in patients who have had congestive failure before operation even though all manifestations of decompensation have been controlled satisfactorily before surgery. Occurrences of this kind probably have not been too uncommon in the past and undoubtedly have been a factor in furthering the errone-

ous belief that patients who have coronary heart disease are extremely poor surgical risks.

Pneumonia, atelectasis, thromboembolic accidents, and abdominal distention during the postoperative period constitute especially great dangers for patients who have coronary heart disease and may be responsible for the development of congestive failure, coronary failure, or acute nonthrombotic myocardial infarction. The antibiotic drugs, early ambulation, use of elastic stockings, prompt administration of anticoagulants on the first appearance of evidence of phlebothrombosis or pulmonary embolism, and continuous gastric suction have greatly reduced the incidence of these complications and have therefore improved the outlook of patients with coronary disease who require surgery.

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